Special Article

Review on Pathophysiology and Treatment of Diabetic Kidney Disease

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Diabetes is the leading cause of chronic kidney disease, which in the Thailand is the most common cause of end stage renal disease (ESRD) requiring dialysis. Patients with diabetic kidney disease (DKD) are at a higher risk of mortality, mostly from cardiovascular complications, than other patients with diabetes. The development of DKD is determined by environmental and genetic factors. This review focuses on the latest published data dealing with mechanisms and treatment of DKD. DKD has several distinct phases of development of the disease and hyperglycemia-induced metabolic and hemodynamic pathways are recognized to be mediators of kidney disease. Multiple biochemical pathways have been postulated that explain how hyperglycemia causes tissue damage: nonenzymatic glycosylation that generates advanced glycosylation end products, activation of protein kinase C, and acceleration of the polyol pathway. Oxidative stress also seems to be a theme common pathway. These derangements, along with hemodynamic changes, activate various cytokines and growth factors such as vascular endothelial growth factor, transforming growth factor-β, Interleukin 1 (IL 1), IL-6 and IL-18. Current renoprotective treatments for DKD include optimization of glycemic, blood pressure, lipid and weight control, blockade of the renin-angiotensin system, salt and protein restriction. Multiple intensive interventions reduce cardiovascular events as well as nephropathy by about half when compared with a conventional multifactorial treatment.

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The classification of diabetes was determined into order by the WHO consultation[1] that included type 1, autoimmune and non-autoimmune, with beta-cell destruction; type 2 with varying degrees of insulin resistance and insulin hyposecretion; gestational diabetes mellitus; and other types where the cause is known (*e.g.* MODY, endocrinopathies). These metabolic changes are associated pathologically with specific microvascular diseases secondary to accelerated atherosclerosis and various other long-term complications, including diabetic retinopathy, nephropathy, and neuropathy. Diabetic kidney disease (DKD) represents the most common cause of end stage renal disease (ESRD) in the United States and Thailand and patients with DKD are at a higher risk of mortality, mostly from cardiovascular complications, than other patients with diabetes.

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Development of DKD

DKD has several distinct phases of development of the disease. Clinical stage of DKD is generally divided into five grades in most guidelines (Table 1) mainly based on the proposal by Mogensen et al[2]. The persistent albumin excretion between 30 and 300 mg/day (20 to 200 mg/min) is defined as microalbuminuria. The presence of microalbuminuria is associated with an increased risk of developing cardiovascular disease and progression of renal disease[3]. Values above 300 mg/day (200 mg/min) of albuminuria are considered to represent overt nephropathy. Once overt proteinuria occurs, the rate of loss of glomerular filtration rate (GFR) and the deleterious effect of hypertension are seen in both type 1 and type 2 diabetes. Most studies dealing with the natural history of DKD have demonstrated a relentless, often linear but highly variable rate of decline in GFR ranging from 2 to 20 mL/min/year, mean 12 mL/min/year[4]. In the absence of aggressive intervention, the time to progression from

Table 1. Clinical stages of DKD

	Albuminuria	Duration	Hypertension	Glomerular filtration rate
Stage 1 Hyperfiltration	< 30 mg/day	onset	normal	increase 20-50%
Stage 2 Silent stage or normoalbuminuria	< 30 mg/day	2-5 years	normal	normal or increase
Stage 3 Incipient or microalbuminuria	30-300 mg/day	5-15 years	high	normal
Stage 4 Overt nephropathy or macroalbuminuria	>300 mg/day	10-20 years	high	decrease 12-15 mL/min/years
Stage 5 End stage renal disease		20-30 years	high	< 10-15 mL/min

overt proteinuria to ESRD in either form of diabetes averages six to seven years. Overall, a faster rate of decline in GFR is associated with higher levels of albuminuria, glycosylated hemoglobin (HA1C), and blood pressure.

Epidemiology

According to estimates by the International Diabetes Foundation, by the year 2025, the frequency of diabetes is expected to increase 3-fold worldwide[5]. The epidemiology of DKD has been best studied in patients with type 1 diabetes, because the time of clinical onset is usually known. The onset of overt nephropathy in type 1 diabetes is typically between 10 and 15 years after the onset of the disease. Epidemiologic studies have shown that 20-40% of the patients with diabetes develop nephropathy, irrespective of glycemic control[6] and the high prevalence of DKD patients (42.9%) in the Thailand was also reported[7]. Recent evidence suggests that the renal risk is currently equivalent in type 1 and type 2 diabetes. The development and progression of nephropathy among almost 5,100 patients with type 2 diabetes enrolled in UKPDS. The yearly rate of progression from diagnosis to microalbuminuria, from microalbuminuria to overt nephropathy, and from overt nephropathy to an elevated plasma creatinine concentration or renal replacement therapy was 2.0, 2.8 and 2.3 percent[8]. In Thai population, the prevalence of microalbuminuria, macroalbuminuria, and ESRD or requirement for renal replacement therapy was 19.7, 23.2, and 0.47 percent, respectively[7].

Risk Factors

Only 1 in 3 patients with diabetes ever developed DKD, both environmental and genetic factors have been postulated as the risk factors that determine who develops hyperglycemia-related renal injury. It has been reported that hyperglycemia, hypertension, obesity, smoking, race (Mexican American/Pima Indians) and genetic predisposition are the main risk factors for the development of DKD. However, select individuals with diabetes were at differential risk for DKD on the basis of family-based studies[9,10]. It is thought that specific genetic backgrounds might influence DKD development. There is growing evidence for the role of genetic factors in the development of DKD[11].

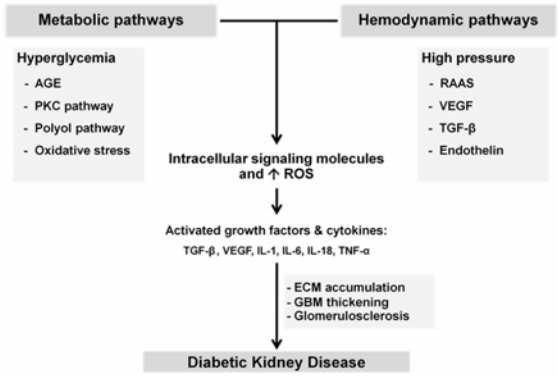
Genetic susceptibility

The importance of genetic factors in the pathogenesis of DKD is suggested by the observation that the likelihood of developing DKD is markedly increased in patients with a diabetic sibling or parent who has DKD[12]. Genetic susceptibility is an important determinant of both the incidence and severity of DKD. Genome wide association analysis has played an important role in identifying several chromosomal regions that likely contain DKD susceptibility genes, and association analyses have evaluated positional candidate genes under these linkage peaks. Some of these loci are in genes involved in complications of diabetes. As an example, a genome wide scans for microvascular complications in Pima Indians with type 2 diabetes, four loci on chromosomes 3, 7, 9 and 20 were identified[13]. Candidate-gene-based association studies have been the most common approaches employed to identify susceptibility genes for DKD. The genes encoding for angiotensin-converting enzyme (ACE), angiotensin II (Ang II) receptor,

glucometabolism, lipids, extracellular matrix and inflammatory cytokines have been selected to test for an association with DKD based on the pathogenesis of disease. The apolipoprotein E gene (ApoE) on chromosome 19q has also been associated with susceptibility to type 1 diabetes[14] and type 2 diabetes[15]. ApoE binds with high affinity to the low density lipoprotein (LDL) receptor and facilitates endocytosis of the associated lipoprotein particle. ApoE has common alleles, E2, E3, and E4, coding for the 3 isoforms of ApoE proteins: ApoE2 ($Arg^{158} \rightarrow Cys$), ApoE3 (parent isoform) and ApoE4 ($Arg^{112} \rightarrow Cys$), respectively. The results of author's study in Thai adults provide data regarding the ApoE polymorphisms associated with DKD, independent of the effect of ApoE genotypes on plasma cholesterol and triglyceride-rich lipoproteins. ApoE4 genotype is associated with protection from type 2 DKD and E2 allele has increased risk of developing type 2 overt DKD.

Pathophysiology of DKD

Hyperglycemia is a most important factor in the progression of DKD. Early functional changes in DKD include glomerular hyperfiltration, glomerular and tubular epithelial hypertrophy and the development of microalbuminuria, followed by the development of glomerular basement membrane (GBM) thickening, accumulation of mesangial matrix and overt proteinuria, eventually a leading cause of glomerulosclerosis and ESRD.



AGE: advanced glycation end products, IL-1: interleukin-1, IL-6: interleukin-6, IL-18: interleukin-18, PKC: protein kinase C, RAAS: renin angiotensin aldosterone system, ROS: reactive oxygen species, TGF-β: transforming growth factor-beta, TNF-α: tumor necrotic factor-alpha, VEGF: Vascular endothelial growth factor.

Fig. 1 Pathways involved in the development of DKD

Hyperglycemia-induced metabolic and hemodynamic pathways are recognized to be mediators of kidney injury (Fig. 1).

Hemodynamic pathways

The hemodynamic factors implicated in the pathogenesis of DKD include increased systemic and intraglomerular pressure and activation of various vasoactive hormone pathways, including the renin-angiotensin-aldosterone system (RAAS), prostanoids, nitric oxide, vascular endothelial growth factor (VEGF), prostanoids, nitric oxide, and endothelins. In response, secretion of profibrotic cytokines, such as transforming growth factor-beta (TGF-β), is increased and further hemodynamic changes occur. Blockade of the RAAS antagonizes the profibrotic effects of Ang II by reducing its stimulation of TGF-β1. Additionally, the administration of an ACE inhibitor to patients with DKD lowered serum concentrations of TGF-β1[16]. These hemodynamic changes play an important role, being present early in the disease and then being exacerbated albumin leakage from glomerular capillaries, overproduction of mesangial cell matrix, podocytes injury and nephron loss[17].

Metabolic pathways

The glucose transport activity is an important modulator of extracellular matrix formation by mesangial cells. Glucose transporter-1 (GLUT-1) regulates glucose entry into renal cells. Glucose and its metabolites subsequently activate metabolic pathways, and these pathways contribute to mesangial expansion and mesangial cell matrix production, mesangial cell apoptosis and structural changes[18]. This may result from a similar increase in the mesangial cell glucose concentration, since similar changes in mesangial function can be induced in a normal glucose milieu by overexpression of GLUT1[19]. Multiple biochemical pathways have been postulated that explain how hyperglycemia causes tissue damage: nonenzymatic glycosylation that generates advanced glycosylation end products (AGE), activation of protein kinase C (PKC), and acceleration of the polyol pathway. Oxidative stress also seems to be a theme common pathway. These derangements, along with hemodynamic changes, may activate various cytokines and growth factors such as VEGF, TGF-β, Interleukin 1 (IL-1), IL-6 and IL-18 and tumor necrosis factor-alpha (TNF-α). In combination, these pathways ultimately lead to increased renal albumin permeability and extracellular matrix accumulation, resulting in increasing proteinuria,

glomerulosclerosis and ultimately tubulointerstitial fibrosis.

Nonenzymatic glycosylation

Glycosylation of tissue proteins contribute to the development of DKD and other microvascular complications. In chronic hyperglycemia, some of the excess glucose combines with free amino acids on circulating or tissue proteins. This nonenzymatic process initially forms reversible early glycosylation products and later irreversible AGEs. The AGEs increase the accumulation of matrix proteins in the glomerular epithelial cells, associated with a concomitant depression in collagenase activity and functional defect in the permselective properties of the glomerular epithelial cells tight junctions, which can contribute to the associated DKD[20]. Moreover, AGEs can be involved in the pathogenesis of DKD by altering signal transduction via alteration in the level of soluble signals, such as cytokines, connective tissue growth factor and free radicals as well as interaction with the AGE receptor on endothelial cells, monocytes, mesangial cells and podocytes[20].

PKC pathway

PKC is an intracellular signaling molecule and activation of it is a major signaling pathway for TGF-b to induce extracellular matrix production in DKD[21]. Hyperglycemia leads to PKC activation involves *de novo* formation of diacylglycerol, AGE and oxidative stress. Furthermore, activation of PKC pathway also leads to increased secretion of vasodilatory prostanoids, which contributes to glomerular hyperfiltration and activates mitogen-activated protein kinase (MAPK), which is called the PKC-MAPK pathway. Recently data obtained by analyzing PKC isoform-specific knock-out mice and use of the PKCb inhibitor ruboxistaurin suggest that the diabetes-induced activation of PKCa is crucial for the development of albuminuria, whereas PKCb activation is important for mesangial expansion, GBM thickening and renal hypertrophy[22].

Polyol pathway

The polyol pathway is involved in the pathogenesis of DKD. A potential link between the formation of sorbitol from glucose catalyzed by aldose reductase in tissues of diabetic patients and the development of DKD was recognized. A number of studies have shown a decrease in urinary albumin excretion in animals administered aldose reductase inhibitors[23].

Oxidative stress

Oxidative stress is increased in diabetes and the overproduction of reactive oxygen species (ROS) in diabetes by the mitochondrial electron transport chain is a direct consequence of hyperglycemia[24]. Several studies show increase in the markers of oxidative stress in type 1 and type 2 diabetes when compared to healthy age-matched subjects[25,26]. ROS mediate many biological effects, including peroxidation of cell membrane lipids, oxidation of proteins, renal vasoconstriction and damage to DNA. In addition to their ability to directly inflict macromolecular damage, ROS can function as signaling molecules to increase activity of nuclear factor-kappaB and interaction with the above three metabolic pathways that cause cellular damage. Activation of PKC pathway, AGE formation, TGF-β and Ang II leads to a furtherance in oxidative stress through increased generation of ROS[27]. Concentrations of markers of DNA damage induced by ROS are higher in patients with more-severe nephropathy. Furthermore, histological analysis of diabetic kidney specimens has accumulated products of glyco-oxidation and lipoxidation in the expanded mesangial matrix and nodular lesion, whereas these lesions are much less common in specimens from patients without diabetes[28].

Inflammatory cytokines

Although multiple metabolic pathways are proposed as the major mediators of DKD, chronic inflammation and activation of the immune system are involved in the pathogenesis of diabetes and its microvascular complications. Recent studies suggest that an inflammatory mechanism mediated by macrophages and angiogenesis may play important roles in the pathogenesis of DKD. Increased accumulation of monocytes/ macrophages in glomeruli has been demonstrated in diabetic kidney lesion. Inflammatory cytokines and growth factors, mainly VEGF, TGF-β, IL-1, IL-6, and IL-18, as well as TNF-α, are also involved in the development and progression of DKD[29].

VEGF

The degree of neovascularization was significantly increased in patients with DKD and hyperglycemia stimulates increased VEGF expression. The high expression of VEGF induces to DKD by promoting vascular permeability, endothelial cell

proliferation and migration, reducing transendothelial electrical resistance, and activation of matrix-degrading protease[30,31]. Moreover, it has been reported the therapeutic efficacy of VEGF inhibitor, which improves albuminuria in an experimental model of DKD[32-34].

TGF-β

TGF-β is a profibrotic growth factor involved in the expansion of mesangial matrix and glomerular hypertrophy in the DKD[35]. Hyperglycemia also increases the expression of TGF-β in the glomeruli of streptozotocin-diabetic rats[36]. Serum and urinary TGF-β levels have been also demonstrated to correlate with the severity of microalbuminuria. In additional, previous study showed that neutralizing inhibition of TGF-β prevented renal atrophy, mesangial matrix expansion, and decline of renal function in an experimental model of DKD[37]. Certain TGF-β inducible genes, such as connective tissue growth factor and heat shock protein 47, appear to exert fibrogenic effects on diabetic kidneys[38,39]. TGF-β may contribute to both the cellular hypertrophy and enhanced collagen synthesis that are seen in DKD.

Interleukin and TNFα

IL-1, IL-6 and IL-18 and TNF-α were increased in models of DKD and seemed to affect the disease via multiple mechanisms. In addition, raised levels of several of these cytokines in serum and urine correlate with progression of nephropathy, indicated by increased urinary albumin excretion. IL-1 alters the expression of chemotactic factors and adhesion molecules, alters intraglomerular hemodynamic, and increases vascular endothelial cell permeability. IL-6 has a strong association with the development of GBM thickening as well as also correlates with albuminuria in type 1 and 2 diabetes[40]. IL-18 leads to production of other inflammatory cytokines, upregulation of intercellular adhesion molecule-1 (ICAM-1), as well as apoptosis of endothelial cells[41]. In addition, IL-18 is a potent inflammatory cytokine that induces IFN-α, which in turn induces functional chemokine receptor expression in mesangial cells[42]. TNF-α is a proinflammatory cytokine with diverse actions, including increased production of endothelial cell adhesion molecules and IL-6, and directly increases endothelial permeability[43].

Renal pathology

Renal pathological changes are observed in patients with long-standing diabetes before the onset of microalbuminuria. There are three major histologic changes in the glomeruli in DKD: mesangial expansion; GBM thickening; and glomerular sclerosis, which may have a nodular appearance (the Kimmelstiel-Wilson lesion). Thickening of the GBM is the first change that can be noted. Afferent and efferent glomerular arteriolar hyalinosis can also be demonstrated within 3 to 5 years after onset of diabetes. Arteriolar hyalinosis, glomerular capillary subendothelial hyaline (hyaline caps), and capsular drops along the epithelial parietal surface of the Bowman capsule make up the so-called exudative lesions of DKD. Marked renal extracellular basement membrane accumulation resulting in extreme mesangial expansion and GBM thickening are present in the majority of diabetic patients with overt nephropathy[44]. In addition, podocyte number are reduced in patients with DKD and decreased glomerular podocyte number and detachment has been related to glomerular permeability alterations in diabetes[45]. The pathologies of DKD in patients with proteinuria are shown in Table 2.

Non-DKD

Proteinuria in patients with diabetes is occasionally due to a glomerular disease other than

Table 2. Pathology of DKD in Patients with Proteinuria

Light microscopic
- Mesangial expansion
- Diffuse GBM thickening
- Nodular glomerulosclerosis (Kimmelstiel–Wilson nodules)
- Mesangiolysis and glomerular microaneurysms
- Fibrin cap
- Capsular drop
- Afferent and efferent hyaline arteriolosclerosis
- Interstitial fibrosis and tubular atrophy
- Interstitial mononuclear inflammatory cell infiltrate
Immunofluorescence
- Linear staining of the GBM and tubular basement membrane for immunoglobulin (Ig) G and albumin
- Non-specific staining for IgM and C3 in sclerotic nodules
- Variable staining of both kappa and lamda light chains
Electron microscopy
- Mesangial expansion by matrix and increased mesangial cellularity
- Diffuse GBM thickening
- Diabetic fibrillosis
- Podocytopenia
- Diffuse foot process effacement
- Electron-dense areas of hyalinosis in sclerotic nodules

DKD. The clinical points suggesting non-DKD are onset of proteinuria less than five years from the detected onset of diabetes in type 1 diabetes, but the time of onset is often difficult to ascertain in type 2 diabetes, presence of an active urine sediment containing dysmorphic red blood cells and cellular casts, acute onset of renal disease and/or rapidly progressive disease characterized by increases in protein excretion and the serum creatinine concentration, clinical signs and/or symptoms of another systemic disease and in type 1 diabetes, the absence of diabetic retinopathy or neuropathy. Proteinuria in diabetic patients with previous clinical points should be thoroughly evaluated for other renal diseases and renal biopsy for diagnosis and prognosis should be strongly considered.

Treatment of DKD

The rate of kidney function decline after the development of nephropathy is highly variable between patients and is influenced by additional factors, including glycemic, blood pressure, and albuminuria control.

Glycemic control

Clinical practice guidelines for the management of DKD issued recommend the HA1C < 7%. However, the efficacy of glycemic control depends in part upon the stage at which it is begun and the degree of normalization of glucose metabolism. Glycemic control can partially reverse the glomerular hypertrophy and hyperfiltration that are thought to be important pathogenic pathways for DKD and decrease the incidence of new-onset microalbuminuria in retrospective[46] and prospective studies of patients with diabetes[47,48]. Progression of established overt nephropathy can also be stabilized or retarded through strict glycemic control, although results of studies assessing this outcome were not uniform[49]. Interestingly, the benefits of glycemic control after pancreas transplantation in patients with type 1 diabetes were observed that mesangial matrix volume, the thickening of glomerular and tubular basement membranes and nodular glomerular lesions were significantly decreased and/or returned to normal as compared to the same measurements at zero and ten years[50,51]. The benefit of glucose control on progression in patients with DKD who have advanced kidney disease is less well studied.

Peroxisome proliferator-activated receptors (PPAR)-gamma agonists

PPAR which are ligand-activated transcription factors, appear to have a role in regulating adipogenesis, lipid metabolism, insulin sensitivity, inflammation, and blood pressure. Previous study in animal models of DKD showed that PPAR-gamma agonists can reduce mesangial proliferation, inflammation and apoptosis[52,53] that are thought to be the pathobiologic mechanism in the development of DKD. While the human data on outcomes are limited, PPAR-gamma agonists reduce urinary albumin excretion at various stages of nephropathy[54-56]. Further studies of longer duration are required to detect a renoprotective effect of these agents.

Blood pressure control

The recommended thresholds to initiate treatment to lower blood pressure are 130/80 and 125/75 mmHg for patients with diabetes and nephropathy, respective. The RAAS has key regulatory functions for blood pressure and fluid homeostasis. In particular, Ang-II, the main effector of the RAAS system, enhances vascular tone of both afferent and efferent glomerular arterioles, eventually regulating the intraglomerular pressure. Beside these hemodynamic effects, activation of Ang II type 1 receptors can trigger expression and release a range of proinflammatory and profibrotic mediators implicated in the progression of DKD[57]. Studies have shown that ACE inhibitors and Ang II receptor blockers (ARB) are superior to the other drugs in reducing disease progression in diabetic patients with nephropathy, making them the drugs of choice[58].

Type 1 diabetes

The benefit of antihypertensive therapy with an ACE inhibitor in type 1 diabetes can be demonstrated in normotensive type 1 diabetes with microalbuminuria and overt nephropathy. ACE inhibitor therapy significantly impeded progression to clinical proteinuria and prevented the increase in albumin excretion rate in nonhypertensive patients with type 1 diabetes and persistent microalbuminuria[59,60]. A more benefit was documented in a randomized, controlled trial comparing captopril with placebo in patients with type 1 diabetes in whom urinary protein excretion was $\geq$ 500 mg per day and the serum creatinine concentration was $\leq$ 2.5 mg/dL[61]. At the end of study, captopril treatment can protect against deterioration in renal function, and reduce the risk of the combined end points of death, dialysis, and transplantation in type 1 diabetes with overt nephropathy and is significantly more effective than blood-pressure control alone[61]. In addition,

patients with type 1 diabetes and nephrotic range proteinuria have demonstrated in clinical remission with substantially lower proteinuria with aggressive control of systemic blood pressure, particularly with ACE inhibitors[62].

Type 2 diabetes

Tight blood pressure control is important for preventing progression of DKD and other complications in patients with type 2 diabetes.

ARB

Two major trials have demonstrated a clear benefit of blood pressure control with ARBs in patients with type 2 diabetic nephropathy. In the Irbesartan Diabetic Nephropathy Trial (IDNT), 1715 hypertensive patients with nephropathy due to type 2 diabetes were randomly treated to irbesartan (300 mg daily), amlodipine (10 mg daily), or placebo. Treatment with irbesartan was associated with a risk of the primary composite end point (doubling of the plasma creatinine, development of ESRD, or death from any cause) that was 23 and 20 percent lower than with amlodipine and placebo, respectively ($p < 0.05$)[63]. In the Reduction of End point in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial, 1513 patients with DKD were randomly assigned to losartan (50 titrating up to 100 mg once daily) or placebo, both in addition to conventional antihypertensive therapy. At 3.4 years, Losartan reduced the incidence of a doubling of the serum creatinine concentration (risk reduction, 25 percent; $p = 0.006$) and ESRD (risk reduction, 28 percent; $p = 0.002$)[64]. In addition, both studies showed that the benefit of ARBs exceeded that attributable to changes in blood pressure.

ACE inhibitor

ACE inhibitors have been demonstrated the benefit of renoprotection in patients with type 2 diabetes, compared with placebo and/or ARBs. The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial compared the use of a fixed combination of perindopril and indapamide to placebo in almost type 2 diabetic patients with normoalbuminuria[65]. At 4.3 years, the patients treated with active therapy had a significant reduction in the rate of new onset microalbuminuria (19.6 versus 23.6 percent) and in the combined end point of new onset or worsening of microalbuminuria or proteinuria[66]. However, there was a significant difference between the groups in mean blood pressure after treatment. Similarly, the Bergamo Nephropathy Diabetic Complication Trial (BENEDICT) demonstrated that the trandolapril, as compared with other antihypertensive therapies, reduced the risk to develop microalbuminuria in hypertensive patients with type 2 diabetes and normoalbuminuria over a period of 3 years[67]. This effect exceeded what could be expected on the basis of blood pressure reduction. The Diabetics Exposed to Telmisartan and Enalapril (DETAIL) trial was a randomized controlled trial that compared enalapril to the telmisartan in 250 patients with early nephropathy as defined by albuminuria (82 percent microalbuminuria and 18 percent macroalbuminuria)[68]. At 5 years, both groups had similar findings for the decline in the GFR, blood pressure, serum creatinine, urinary albumin excretion, ESRD, cardiovascular events, and mortality. The results support the clinical equivalence of ARBs and ACE inhibitors in diabetic patients with microalbuminuria.

ACE inhibitor plus ARB

Dual blockade of the RAAS with both an ACE inhibitor and an ARB is superior to either therapy alone in decreasing proteinuria with DKD[69,70]. However, long-term trials are needed to further establish the role of dual blockade of the RAAS in slowing disease progression. Additional concern about dual blockade of the RAAS were reported recently from the Ongoing Global Endpoint Trial (ONTARGET) trial, the combination therapy reduced proteinuria and prevented new onset of micro- and macroalbuminuria to a greater extent than did monotherapy, but the combination of the two drugs in patients at high vascular risk was associated with more composite end points including the need for acute dialysis, doubling of serum creatinine, and death, than use of the single agents alone[71].

ARB plus aliskiren

The newest RAAS-blocking agent is aliskiren, an oral direct renin inhibitor. The Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) trial, patients received 100 mg of losartan daily, patients were randomly assigned to receive 6 months of treatment with aliskiren (150 mg daily for 3 months, followed by an increase in dosage to 300 mg daily for another 3 months) or placebo[72]. Aliskiren may have renoprotective effects patients were started aliskiren plus losartan was associated with a significant 20 percent greater reduction in proteinuria compared to

losartan alone, that are independent of its blood-pressure-lowering effect in patients with hypertension. Further studies are needed to demonstrate a beneficial effect of aliskiren on the important long-term renal outcomes of loss of GFR and progression of ESRD.

Aldosterone receptor antagonists

Experimental studies supporting aldosterone antagonists have been shown anti-inflammatory mechanism, ant-fibrotic properties and suppression of markers of tubular injury, interstitial fibrosis and glomerulosclerosis[73]. Aldosterone antagonists have generally been considered to have an antiproteinuric effect, and addition of spironolactone to an ACE inhibitor or ARB is associated with a marked and sustained antiproteinuric effect, with the rate of hyperkalemia being similar to placebo[74-76]. These results are based on studies with small numbers of patients that were mostly of very short duration of follow-up. There are no long term data regarding benefit with the combination of ACE inhibitor or ARB and aldosterone antagonists in terms of slowing the progression of DKD. Moreover, some studies showed that serum potassium levels increased significantly with combinations of aldosterone antagonists and ACE inhibitor/ARB[77]. In clinical practice, the use of this combination of agents in patients with low GFR should be undertaken with careful instructions for dietary potassium restriction and avoidance of nonsteroidal anti-inflammatory drugs and cyclooxy-genase-2 inhibitors

Lipid control

Hyperlipidemia is common in diabetic patients, a tendency that is increased by the development of chronic kidney disease (CKD). Experimental studies have shown that circulating lipoproteins contribute to the development of glomerulosclerosis and tubulointerstitial damage. The applicability of these findings to DKD is uncertain. Lipid-lowering agents (statins) showed renoprotection in a variety of proteinuric glomerular diseases[78]. A recent meta-analysis reported a beneficial effect of statins in patients with albuminuria[79]. The renoprotective effects of these agents may be ascribed to the LDL-lowering effects as well as to their pleiotropic actions. In the Diabetes Atherosclerosis Intervention Study (DAIS), all type 2 diabetic patients were randomly assigned to fenofibrate or placebo[80]. Improvement in lipid profiles with fenofibrate in patients with type 2 diabetes was associated with reduced proteinuria and progression from normal albumin excretion to microalbuminuria. Possible mechanisms of benefit with fenofibrate may be related to the activation of PPAR-alpha in mesangial cells[81]. The progression of DKD may be significantly affected by treatment of dyslipidemia.

Other agents

Current therapeutic interventions include optimization of glycemic, blood pressure and lipid control, but more innovative strategies are needed for the prevention and treatment of DKD. Specific pharmacological agents for the treatment of patients with established DKD are not available for clinical use, but several new agents are studied in clinical trials. A variety of other agents have been effectively ameliorated kidney damage and/or injury markers in many experimental models of DKD, including endothelin receptor antagonists, PKC inhibitors (ruboxistaurin), vasopeptidase inhibitors, AGE inhibitors (aminoguanidine), glycosaminoglycans (sulodexide) and TGF-β inhibitors[82]. Large-scale clinical trials will be needed to confirm safety and to validate prospective benefits of these agents on relevant clinical endpoints in DKD.

Protein restriction

The benefit of restriction of dietary protein in patients with DKD is uncertain. Two small controlled trials demonstrated that dietary restriction of protein (0.6 g/kg per day) and phosphorus retarded the progression of renal failure in patients with type 1 diabetes who have nephropathy[83,84]. In contrast, a prospective, controlled trial was performed comparing the effects of a low-protein diet (0.89 g/kg/day) with a usual-protein diet (1.02 g/kg/day) in 82 type 1 diabetic patients with nephropathy. At 4 years, the mean declines in GFR were 3.9 mL/min/year in the usual-protein diet group and 3.8 mL/min/year in the low-protein diet group. However, the relative risk of ESRD or death was 0.23 (0.07 to 0.72) for patients assigned to a protein restriction[85].

Salt restriction

DKD patients have a high prevalence of hypertension, increased total body exchangeable sodium levels, and an impaired ability to excrete a sodium load. Salt restriction and/or diuretics enhance the effect of RAAS blockade on proteinuria in proteinuric CKD patients[86]. Some evidences have also shown that a low-sodium diet potentiates the antihypertensive and antiproteinuric effects of

antihypertensive agents in diabetes[87,88]. Thus, ensuring that patients who receive on ACE inhibitors or ARBs treatment are on a low sodium diet (< 90 mEq/day) and taking an appropriate diuretic should increase the likelihood of achieving the antiproteinuric efficacy of anti-hypertensive agents. An assessment of baseline sodium intake can be undertaken by obtaining a 24-hour urine for sodium and creatinine.

Weight reduction

In Diabetes Control and Complications Trial (DCCT), waist circumference was found to predict the development of microalbuminuria during the 8 years follow-up period[89]. It has been also reported that obese diabetic patients who lose weight significantly decreases in proteinuria[90]. Although no significant differences in renal function were reported in these patients, the length of follow-up was probably too short to have observed such an effect. Additional clinical trial might be informative regarding the effects of weight loss on inflammatory markers and on DKD progression.

Intensive combined therapy

The optimal therapy of DKD continues to evolve. It now seems clear in targeting of a therapeutic regimen to achieve blood pressure and blood glucose goals, both lower protein excretion and slow the rate of disease progression in DKD patients. Dietary protein and salt restriction, weight reduction, aggressive lipid lowering, stop smoking and exercise may be beneficial in patients with established DKD. The Steno-2 study had evaluated the impact of long-term intervention comprising combined behavior modification, tight glucose regulation and the use of RAAS blockers, aspirin, and lipid-lowering agents in patients with type 2 diabetes. During the 13.3 years of follow-up of patients with type 2 diabetes and microalbuminuria, all-cause death was significantly reduced in the intensive treatment group (30%) compared with the conventionally treated group (50%)[91]. Furthermore, risk reductions in patients receiving intensive intervention were seen for the development of nephropathy as well as for the development or progression in retinopathy and autonomic neuropathy by about half[92].

Conclusion

DKD is one of the main causes of ESRD and is associated with elevated cardiovascular morbidity and mortality. Both environmental and genetic factors have been postulated as the risk factors that determine who develops who develops hyperglycemia-related renal injury. DKD occurs as a result of an interaction between hemodynamic and metabolic pathways. Metabolic pathways are also activated within the diabetic kidney and result in accumulation of AGEs, activation of PKC, renal polyol formation and enhanced oxidative stress. These derangements activate various cytokines and growth factors. These mechanisms ultimately lead to renal histologic changes in the glomeruli in diabetic nephropathy: mesangial expansion; GBM thickening; and glomerular sclerosis. The current mainstay of pharmacotherapy involves inhibition of the RAAS with ACE inhibitors and/or ARBs, and glucose-lowering agents. Data from the Steno-2 study provides the best evidence to date of the magnitude of the benefit that can be derived from instituting multiple interventions focusing on risk factor reduction. More innovative strategies that involve pathophysiology mechanism of disease are needed for the prevention and treatment of DKD.

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กลไก พยาธิสรีรวิทยา และแนวทางการรักษาโรคไตจากเบาหวาน

บัญชา สถิระพจน์

เบาหวานเป็นสาเหตุพบบ่อยของเกิดโรคไตเรื้อรัง ซึ่งจากข้อมูลในประเทศไทยพบว่า เบาหวานเป็นสาเหตุส่วนใหญ่ของการเกิดโรคไตเรื้อรังระยะสุดท้าย เมื่อผู้ป่วยเกิดโรคไตจากเบาหวานจะเพิ่มความเสี่ยงต่อการเสียชีวิตโดยเฉพาะจากโรคหัวใจและหลอดเลือด ปัจจัยทางสิ่งแวดล้อม และพันธุกรรมเป็นปัจจัยสำคัญของการเกิดโรคไตจากเบาหวาน บทความนี้ได้ทบทวนวรรณกรรมจากวารสารทางการแพทย์ในปัจจุบันถึงกลไกพยาธิสรีรวิทยา และแนวทางการรักษาโรคไตจากเบาหวาน ขบวนการหลักของการเกิดโรคเกิดจากการเปลี่ยนแปลงทางเมตาบอลิซึม และความดันภายในหลอดเลือดไต การเปลี่ยนแปลงทางเมตาบอลิซึมจากระดับน้ำตาลในเลือดสูงทำให้เกิดพยาธิสภาพไตผ่านขบวนการสร้าง advanced glycosylation end products การตุ้นขบวนการ protein kinase C และขบวนการ polyol แล้วทำให้เกิดภาวะ oxidative stress เชื่อว่าเป็นผลรวมของขบวนการดังกล่าว นอกจากนั้นเกิดการกระตุ้นการสร้าง cytokines และ growth factors ได้แก่ vascular endothelial growth factor, transforming growth factor-b, Interleukin 1 (IL-1), IL-6 and IL-18 ในร่างกายซึ่งเป็นปัจจัยส่งเสริมของการเกิดโรคไตจากเบาหวาน การรักษาโรคไตจากเบาหวานในปัจจุบันเน้นถึงการควบคุมระดับน้ำตาลในเลือด ความดันโลหิต ไขมันในเลือด น้ำหนักตัว จำกัดอาหารเค็ม จำกัดปริมาณโปรตีนในอาหาร และเลือกใช้ยาลดความดันโลหิตในกลุ่มยับยั้งระบบ renin-angiotensin ในร่างกาย การควบคุมปัจจัยดังกล่าวอย่างเคร่งครัดสามารถลดอัตราการเสียชีวิตจากโรคหัวใจและหลอดเลือด และโรคไตจากเบาหวานถึงร้อยละ 50